

### **REMARKS/ARGUMENTS**

Reconsideration of this application is requested. Claims 1-14 and 16-18 will be active in the application subsequent to entry of this Amendment.

The claims have been amended in order to address the formalities issues raised in item 2 of the Official Action and to more particularly point out and distinctly claim that which applicants regard as their invention by directing the claims to preferred embodiments of the description.

Claim 1 is amended to specify the size of the liposomes based upon previous claim 12 and remove the term "submicron". Claim 1 as above revised is consistent with the description of the invention given on page 2, lines 11 and 12. As a consequence of the amendments made to claim 1, claim 12 has been amended and directed to a preferred aspect of the disclosure which may be found at page 8, line 25.

The present application is characterized by a method of preparing triterpenoid-containing liposomes in substantial quantity, incorporated at a high concentration and uniformly into the liposome. This improved "payload" capacity addresses problems previously encountered in the prior art and also not contemplated in the documents cited in the current Official Action (discussed in more detail below). Claim 1 has thus been amended to include a statement of the triterpenoid as falling within the range of 0.001-5% by weight based on the weight of the liposome. This feature was previously in claim 11 and claim 11 has been amended and directed to a preferred aspect of the description as may be found in the last line of page 7.

Claim 17 has been criticized for including mention of "tooth paste" and "oral cleaner" in a claim otherwise directed to a skin care composition. These two aspects of claim 17 have been removed and placed in new dependent claim 18 thereby resolving the examiner's concerns in item 2 of the Official Action.

The object of the present invention is to provide liposomes containing triterpenoid at a high concentration while using non-toxic solvent without intensive mechanical treatment. In order to incorporate triterpenoid at a high concentration uniformly into a liposome, the present invention employs triterpenoid having acid group, and by adding a base, the triterpenoid is transformed into its salt having surface activity. The transformed triterpenoid salt is a surfactant of high HLB, and it forms a mixed micelle system when mixed with low HLB lipid. The

examples of the base are triethanolmaine, triisopropanolamine, potassium hydroxide, 2-aminobutanol, sodium hydroxide, ammonium hydroxide or calcium hydroxide. The above-obtained mixed micelle system maintains its pH in a range of 10-11. By adding an acid to decrease its pH to 5-8, the triterpenoid salt transforms back to the original form having an acid group, and thereby loses its surface activity, and results in changing the mixed micelle system into a liposome. During the transformation, triterpenoid is loaded into the liposome at high concentration (*see* column 2, third paragraph of specification of the present invention).

The balance of the Official Action deals with a series of three separate prior art-based rejections, items 4-6, which are directed to all of the then-pending claims.

None of the cited documents disclose such use of acid and base for the transformation into a mixed micelle system or liposome as in the present invention.

Specifically, Touitou (USP 5,716,638) (D1) merely disclose the use of TEA in the example of a gel preparation, but it does not disclose the reason why TEA is added to the gel preparation. In addition, D1 does not disclose or suggest the combined use of base and triterpenoid of the present invention, i.e., to transform triterpenoid having acid moiety into its salt having surface activity so as to form mixed micelle system with low HLB lipid. Further, D1 does not disclose or suggest the use of acid to transform the triterpenoid salt back into the original form having an acid group, resulting in changing the mixed micelle system into a liposome, whereby triterpenoid is loaded into the liposome at a high concentration.

Cauwenbergh (D2) (USP 5,476,853) merely discloses that the pH of the formulation can be regulated by the addition of a base, acid or buffer; it does not disclose or suggest the transformation of the triterpenoid having acid moiety into its salt and then back into its original form by the subsequent use of base and acid.

The use of TEA in Delrieu (D3) (USP 5,926,015) is to prevent aggregation of the liposomes, which is different from that of the present invention to encapsulate triterpenoid at high concentration. As the purpose is different so too is the function.

Brown et al (D4) (WO 01/17523) does not teach the use of acid and base to encapsulate triterpenoid at high concentration.

Thus, the present invention is considered to be non-obvious over the teachings of the cited documents.

Considering the comments provided in the Official Action, it is not seen that the applied references describe the preparation of triterpenoid-containing liposomes containing the claimed amount of triterpenoid within the liposome. Indeed, the primary reference to Touitou appears to be concerned more with increasing the concentration of the alcohol component in combination with the polyol component as a means for drug delivery and not on the quantity of drug that is actually delivered.

As a general matter, the prior art-based rejections appear to focus on acid-based adjustments and various processing conditions which, it is asserted, would be readily recognized by one having ordinary skill in the art. The examiner comments "Applicant has not shown any unexpected results using the claimed method". In fact, the unexpected results may be regarded as lying in the "payload" of the triterpenoid active ingredient achieved by the process of the present invention. Based upon a perusal of the applied references it appears that increasing payload of the active ingredient is not of concern to the documents applied in the Official Action.

For the above reasons it is respectfully submitted that the claims of this application are in condition for allowance. Reconsideration is requested.

Respectfully submitted,

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